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09/446,543	12/20/1999	SHUJI HINUMA	2472US0P	2478

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EXAMINER

MITRA, RITA

ART UNIT PAPER NUMBER

1653

DATE MAILED: 04/09/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary

Application No.

09/446,543

Applicant(s)

HINUMA ET AL.

Examiner

Rita Mitra

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 5,7-9,12,15 and 16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4,6,10,11,13 and 14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 December 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3. 6) ☐ Other:

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DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1653.

Election/Restriction

Applicants' election with traverse of Group I, claims 1-4, 6, 10, 11, 13 and 14 in Paper No. 12 is acknowledged. Provisional election of sequence SEQ ID NO: 61 and the disease hypooovarianism is also acknowledged.

The traversal is on the ground(s) that the agents and uses thereof identified as the claims of group I and the uses for those same agents identified as the claims of groups II, III, and IV are sufficiently related so as not to unduly burden the Examiner in making a search.

This is not found persuasive because the agents claimed in these groups of inventions are not necessarily the same. For example, agent of group I is for modulating prolactin secretion, which means promote and inhibit prolactin secretion, whereas agents of group II, III and IV are for inhibiting prolactin secretion, for modulating placental function and for diagnosis function of prolactin secretion respectively. The effects of the methods of these groups are distinct from each other and thus represents patentably distinct subject matter. Furthermore, the search burden would be there because of distinct chemical entities of the agents of each group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5, 7-9, 12, 15 and 16 are withdrawn under 37 C.F.R. § 1.142(b) from further consideration by the Examiner, as being drawn to a non-elected invention.

Claims 1-4, 6, 10, 11, 13 and 14 are pending and are under consideration in the instant application. Elected sequence SEQ ID NO: 61 and the disease hypoovarianism is also under examination.

Objection to the Specification

The disclosure is objected to for the following informality:

This application is a 371 of PCT/JP98/02765 filed on June 22, 1998 and the continuing data is not entered in the first page, first line of the specification. An appropriate correction is required.

The abstract of the disclosure is objected to because the abstract is too long, it should be a single paragraph and/or should contain 250 words. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 13 provides for the use of a ligand polypeptide where the claim recites, use of a ligand polypeptide for a G protein-coupled receptor protein for manufacture of a medicament for modulating prolactin secretion, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claim 13 is a nonstatutory claim - a 'use' is not a statutory class of invention.

Claim 13 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 10, 11, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent comprising a ligand polypeptide of full length sequence set forth in SEQ ID NO: 73; does not reasonably provide enablement for a

substantial equivalent of that sequence or fragments generated from any position located on the sequence of SEQ ID NO: 73 or enablement of a sequence set forth in SEQ ID NO: 61. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-4, 6, 10, 11, 13 and 14 encompass an agent for modulating prolactin secretion that comprises a ligand polypeptide, or a salt thereof, for a G protein-coupled receptor protein (claim 1), wherein the ligand polypeptide comprising an amino acid sequence represented by SEQ ID NO: 73, or a substantial equivalent thereto, or its amide or ester or a salt thereof (claim 2), wherein said sequence is represented by SEQ ID NO: 61 (claim 3); an agent of claim 1, for promoting prolactin secretion (claim 4), that agent is for treating or preventing hypoovarianism (claim 6), and for promoting lactation of domestic mammal (claim 10), and for an aphrodisiac (claim 11); use of the ligand polypeptide for manufacture of a medicament for modulating prolactin secretion (claim 13); a method for modulating prolactin secretion in a mammal, which comprises administering to said mammal the ligand polypeptide (claim 14).

The specification, however, only discloses cursory conclusions (see page 4-5), without data to support the findings, which state that the ligand polypeptide of the agent is a polypeptide comprising an amino acid sequence represented by SEQ ID NO: 73 or a substantial equivalent thereto (page 4, lines 11-15). While defining "substantial equivalent" at page 19 specification indicates that it means the binding activity of the ligand and the receptor and physical characteristics are substantially same, and polypeptides containing the substitution, deletion or insertion would be considered to be substantially equivalent to polypeptides lacking the substitution deletion or insertion. There are no indicia that the present application enables the full scope in view of the amino acid sequences corresponding to a 'substantially equivalent' of the sequence as set forth in SEQ ID NO: 73 as discussed in the following stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breadth of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the state of the prior art; and, 8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention:

The nature of the invention is defined by the claims, which include an agent for modulating prolactin secretion that comprises a ligand polypeptide, or a salt thereof, for a G protein-coupled receptor protein, wherein the ligand polypeptide comprising an amino acid sequence represented by SEQ ID NO: 73, or a substantial equivalent thereto, or its amide or ester or a salt thereof (claim 2), wherein said sequence is represented by SEQ ID NO: 61, use of the said ligand for manufacture of medicament for prolactin secretion and a method for modulating prolactin secretion in mammals. The scope of the claims includes use of the agent for treating or preventing hypoovarianism, for manufacturing of a medicament for modulating prolactin secretion and a method for modulating prolactin secretion in a mammal, which comprises administering to said mammal the ligand polypeptide. However the specification does not provide the information on the structure and function of the claimed variants of the said ligand.

2) the breadth of the claims:

The breadth of the claims is broad and encompasses an unspecified amount of variants regarding the ligand polypeptide of SEQ ID NO: 73 and SEQ ID NO: 61 as biological active variants, which are not specifically described or demonstrated in the specification.

Claim 1 and 2 are directed to an agent for modulating prolactin secretion that comprises a ligand polypeptide for a G protein-coupled receptor protein, wherein the ligand polypeptide

comprising an amino acid sequence represented by SEQ ID NO: 73, or a substantial equivalent thereto. The specification describes a ligand polypeptide for G protein-coupled receptor protein and shows the influence of this polypeptide on prolactin secretion (see Examples 46, 47, 49). None of the examples provide any indication that the ligand polypeptide might inhibit prolactin secretion thus part of claim 1 ('inhibition' part of 'modulation') is not enabled by the description. Furthermore no biological activities were attributed to the recited variants and the structural information was limited (see specification page 21, lines 22-36, page 22, lines 1-6). There is no disclosure about the biological activities of the claimed variants. Identification of the ligand polypeptide is described in Example 21 of the specification and its function for promoting prolactin secretion were described in *in vivo* assay of Examples 46, 47, however specification fails to provide any description or demonstration of a variant of ligand polypeptide of SEQ ID NO: 73 or SEQ ID NO: 61 sequence modulating prolactin secretion. For these reasons, it requires undue experimentation to make the claimed invention, especially where in claims 2 and 3, substantial equivalents would have been included by the claims and for which the specification does not describe with particularity as to retention of function. Without any guidance or suggestions a skilled artisan would not be able to predict the structure of a variant that would demonstrate the same activity as the activity of the ligand polypeptide sequence of SEQ ID NO: 73 and SEQ ID NO: 61. Thus, for the reasons set forth above, undue experimentation is required to make and use the claimed fragments.

Claims 6, 10 and 11 are directed to the use of the agent for treating or preventing hypoovarianism (claim 6), for promoting lactation of domestic mammal (claim 10), and for an aphrodisiac (claim 11). However, there is no disclosure of the use of any variant for any treatment or for any induction/influence as claimed for the ligand polypeptide. For these reasons, it requires undue experimentation to make the claimed invention.

Claim 13 is directed to use of the ligand polypeptide for manufacture of a medicament for modulating prolactin secretion. Specification at pages 39-41 describes the pharmaceutical composition comprising the ligand polypeptide, however specification fails to provide any use of the variants for manufacturing of a medicament that modulates prolactin secretion.

Claim 14 is directed to a method for modulating prolactin secretion in a mammal, which comprises administering to said mammal the ligand polypeptide. Specification at pages 67-69 provides a general description of the application of the ligand polypeptide and also describes an administration of the polypeptide (Example 49) to rats that increases prolactin secretion. However specification fails to provide description for the use of the variants of ligand polypeptides in the claimed method. For the reasons set forth above, undue experimentation is necessary to make and use the claimed fragments that retain the property of modulating prolactin secretion.

- 3) the predictability or unpredictability of the art;

The invention is highly unpredictable for the reasons set forth for factors 1 and 2 above.

As to factors 4 through 6,

- 4) the amount of direction or guidance presented;
- 5) the presence or absence of working examples; and
- 6) the quantity of experimentation necessary;

The claims are directed to an agent for modulating prolactin secretion which comprises a ligand polypeptide for a G protein-coupled receptor protein, wherein the polypeptide represents the amino acid sequence set forth in SEQ ID NO: 73 or a substantial equivalent thereto. However, the specification provides only a generic description of how a variety of variants of ligand polypeptide can be generated (page 19-21), no specific guidance is provided on the generation of the fragments that demonstrate the biological activity of the ligand sequences of SEQ ID NO: 73. There are no working examples of these variants in the specification. While the specification in Example 46 and 47 describes and demonstrates that the ligand polypeptide set forth in SEQ ID NO: 73 having prolactin secretion function, there is no disclosure about the biological activities of the claimed variants of ligand polypeptide. Since the specification fails to provide sufficient guidance on the structure and function of the various variants, it is necessary to have additional guidance on the identities of fragments

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to carry out further experimentation to assess their property of having prolactin secretion function. In part, claim 6 requires prevention. Prevention, simply put, means that hypoovarianism does not occur in an individual, not even the first time. This requires undue experimentation on the basis of non-disclosure in the present application specification on how to prevent hypoovarianism.

As to factors 7-8:

- 7) the state of the prior art; and,
- 8) the relative skill of those skilled in the art:

The prior art has shown an agent as well as a ligand polypeptide for a G protein-coupled receptor protein for modulating prolactin secretion (see section below of 103(a) rejection), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structure and function for various amino acid sequences to be considered enabling for variants/fragments for ligand polypeptide. Furthermore, prior art demonstrates the enablement of a specific ligand polypeptide that couples with a specific G protein-coupled receptor to modulate prolactin secretion, prior art doesn't describe the enablement of any agent comprising any ligand polypeptide that binds with any G protein-coupled receptor protein to modulate the prolactin secretion as claimed in the instant application.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because in summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable for the various modified forms, it is necessary to have additional guidance and to carry out further experimentation to assess the property of the variants. Therefore, due to large quantity of experimentation necessary to determine an activity or property of the disclosed ligand polypeptide and the fragments thereof, such that it can be determined how to use the claimed ligand polypeptide, the lack of direction/guidance presented in the specification regarding same,

the absence of working examples directed to same, the complex nature of the invention, the specification fails to teach the skilled artisan how to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-4, 6, 10, 11 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the use of the term “modulating.” The term “modulating” renders the claim indefinite, it is unclear whether the agent may as well promote as inhibit prolactin secretion. Claims 1 and 14 are indefinite because it is not clear whether or not all polypeptides that bind to all G-protein coupled receptor proteins would have effected modulation of prolactin secretion or is it only a G protein coupled receptor protein and particular ligand. Claims 2 and 4 are included in the rejection because they are dependent on rejected claim and do not correct the deficiency of the claim from which it depends.

Claims 2 and 3 are indefinite because of the use of the term “represented.” The term “represented” renders the claim indefinite because it is not clear what are those amino acids of SEQ ID NO: 73 and SEQ ID NO: 61 respectively that are represented in these claims.

Claim 2 is indefinite because of the use of the expression “substantial equivalent.” The expression “substantial equivalent” renders the claim indefinite because it is not clear what is

the position of the sequence of said 'equivalent' in relation to the sequence of SEQ ID NO: 73. It is also not clear whether the claimed 'equivalent' has the same function of SEQ ID NO: 73.

Claim 3 is included in the rejection because it is dependent on rejected claim and does not correct the deficiency of the claim from which it depends.

Claim 6 is indefinite as to whether or not the agent is equally effective across the range of recited disease states and it is also not clear how recitation of the diseases alters or makes the "agent" any different in physical and chemical properties and biological function. However, from the recited diseases only 'hypoovarianism' is elected therefore an appropriate correction is required.

Claim 10 is unclear because how the agent differs between that for "domestic" instead of "non domestic" mammal. Claim 10 compared to claim 4 and claim fail to define any particular physical, chemical and biological properties to distinguish the the agent as to difference based on disease treated as recited in claim 6 and domestic compared to nondomestic mammals.

Claim 11 is indefinite as to any change in chemical, biological or physical property necessary to function as a recited "aphrodisiac."

Claim 14 is indefinite because it lacks essential steps as claimed in the method for modulating prolactin secretion in a mammal. The omitted steps are: the site and method of administration, the therapeutically effective amount of the agent and a step whereby the desired outcome using the claimed polypeptide can be determined.

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kask et al. (Life Sciences, 1997, vol. 60, No. 18, pp 1523-1533) taken with; Zheng et al. (American Journal of Physiology, 1997, vol. 272, pp E282-287); and Lasa et al. (Molecular and Cellular Endocrinology, 1997, vo. 130 (1, 2), pp 93-100).

Kask et al. teach a neuroendocrine peptide, Galanin, which binds to, and acts on specific G-protein coupled receptors (see summary, page 1523) of pituitary cells (see Table 1 and page 1528, fifth paragraph, lines 4-7), and stimulates prolactin secretion (see summary, Table 1, page 1528, fifth paragraph, lines 4-7). This addresses claims 1 and 4 of instant application. However,

Kask et al. do not teach a ligand polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 73 or 61 as claimed in claim 2 and 3.

Zheng et al. teach a polypeptide, the alpha-melanocyte-stimulating hormone (alpha-MSH), which binds to rat pituitary cells to stimulate prolactin secretion (see Abstract, at page E282; col. 1, lines 4-5 at page E284; Fig. 1; and col. 1, lines 1-3 at page E286). Zheng et al. do not specifically teach a G protein-coupled receptor protein, however it is implied that such a hormonal intracellular transduction signal to be mediated by a G protein-coupled receptor protein. This addresses claims 1 and 4 of instant application. Furthermore Zheng et al. do not teach the amino acid sequence of the alpha-MSH. However, it cannot be ruled out that the ligand polypeptide taught by Zheng et al. has the same amino acid sequence of the ligand polypeptide of the instant application, since they have similar characteristics: their binding to the rat pituitary cells induces an increase of prolactin secretion (see Example 46), thus addresses claims 2 and 3.

Lasa et al. teach the heterodimeric G protein Gs that couples several surface ligand receptors to to promote prolactin gene expression in pituitary cells through acyclic camp production mechanism (see abstract at page 93). Lasa et al. also teach an agent lovastatin, which decreases the basal expression of prolactin and that expression is reversed by the addition of mevalonate to the cell culture medium. This addresses claims 1 and 4 of instant application. However, Lasa et al. do not teach a ligand polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 73 or 61 as claimed in claim 2 and 3.

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Thus, the agent comprising a ligand polypeptide for a G protein-coupled receptor protein for modulating prolactin secretion of claims 1-4, from the combined cited references have been obvious since the combined references teach a ligand polypeptide in a manner similar if not identical to that recited in the claims. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

No claim is allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Rita Mitra, Ph.D.
April 6, 2002



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